Total Synthesis of (+)-Epoxyquinols A and B**

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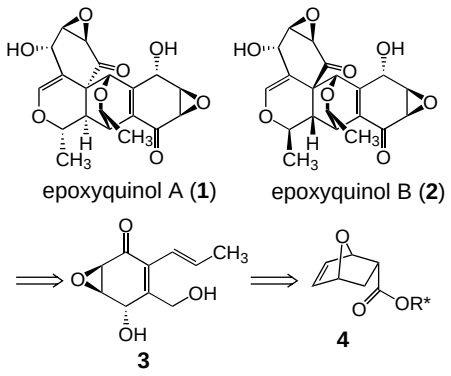
Angiogenesis inhibitors are promising drugs for the treatment of angiogenesis-related diseases such as cancer.[1] We have recently reported the isolation and structural determination of unique pentaketide dimers, epoxyquinols A (**1**)[2] and B (**2**; Scheme 1),[3] which show anti-angiogenic activity, but have different structural properties from the known



Scheme 1. Retrosynthesis of epoxyquinols A(**1**) and B (**2**).

angiogenesis inhibitors. To facilitate elucidation of the mechanism of action of epoxyquinols A and B, the development of a method for their total synthesis and derivatization is highly desirable. Though structurally epoxyquinols A and B have a highly functionalized and complicated heptacyclic ring system containing 12 stereocenters, biosynthetically it is proposed they are formed by an unusual oxidative dimerization of the much simpler epoxycyclohexenone **3** (Scheme 1).[2,3] Herein we report the first total synthesis of the naturally occurring enantiomers of (+)-epoxyquinols A and B using the postulated biomimetic oxidative dimerization, along with determination of their absolute stereochemistry.

The monomer **3** of epoxyquinols A and B was the initial target. The synthesis starts from the Diels–Alder reaction between furan and a chiral dienophile,[4] which is planned in such a way to establish the correct stereochemistry and introduce all the carbon atoms except those in the side chain. Though there are a number of methods for the diastereoselective Diels–Alder reaction of a chiral acrylate ester with furan,[5] few of these are synthetically useful with high *endo/exo* selectivities and diastereoselectivities. The low selectivities can be attributed to rapid *endo/exo* isomerization and/or to a retro-Diels–Alder reaction, which occurs at around −20 °C.[5c] Recently we have found that $HfCl_4$ is a highly efficient Lewis acid in the Diels–Alder reaction of furan, and enables the reaction to proceed at low temperature.[6] Thus, the $HfCl_4$-mediated Diels–Alder reaction of furan was applied to the chiral acrylate ester derived from Corey's chiral auxiliary ((−)-(1*R*,2*R*)-2-(naphthalene-2-sulfonyl)cyclohexanol),[7] in the expectation of high selectivity. In fact, in the presence of $HfCl_4$, the chiral acrylate ester **5** reacted with furan in toluene at low temperature (−45 °C) over 48 h to give the cycloadducts **4** in good yield with moderate *endo/exo* selectivities and high diastereoselectivities (Scheme 2).

The next stage was the preparation of *endo*-epoxide **7**. As an *exo*-epoxide was obtained by the direct epoxidation reaction of **4**,[8] a novel method was developed for the selective formation of the *endo*-epoxide via the iodolactone **6**. Though the usual two-step procedure (hydrolysis and iodolactonization) afforded iodolactone **6** in good yield, the chiral auxiliary was recovered in only 40% yield along with 55% of 1-(naphthalene-2-sulfonyl)cyclohexene. On the other hand, direct treatment of the *endo* isomer with I_2 in aqueous CH_3CN afforded iodolactone **6** in 81% yield with recovery of the chiral auxiliary in 94% yield. After recrystallization, optically pure lactone **6** was obtained, and its absolute stereochemistry was determined by comparing its optical rotation with that in the literature.[9] Though the direct transformation of iodolactone **6** to epoxy methyl ester **7** in MeOH under a variety of basic conditions was unsuccessful, a two-step conversion (hydrolysis and esterification) worked well: Treatment of **6** with KOH in DMF at 60 °C for 10 h, followed by esterification with MeI under sonication conditions for 1 h, furnished **7** in one pot, in high yield (94%).

Exposure of **7** to lithium diisopropylamide (LDA) at −90 °C for 30 min led to β-elimination, affording hydroxy ester **8**. An excess of LDA should be avoided owing to Michael addition of diisopropylamine to **8**, which provides a β-amino ester as a side product. Hydroxyl-directed epoxidation of homoallylic alcohol **8** using a catalytic amount of $[VO(acac)_2]$ (acac = acetylacetonate) and excess *tert*-butyl hydroperoxide (TBHP) under reflux in CH_2Cl_2[10] proceeded to give diepoxide **9** as a single isomer in high yield. Although reduction of ester **9** with diisobutylaluminum hydride (DIBAL) proceeded smoothly, the yield of the diol **10** was quite low owing to its water solubility. Thus, a nonaqueous workup was examined: Reduction with $NaBH_4$ in MeOH at room temperature for 15 min, removal of solvent, and flash column chromatography afforded the diol **10**. The primary alcohol of the diol **10** was selectively protected with *tert*-butyldimethylsilyl chloride (TBSCl), affording **11** in 81% yield over two steps. Though the oxidation of **11** with SO_3·pyridine[11] afforded an epoxyquinone,[12] the over-oxidation product of **12**, the use of the Dess–Martin periodinane[13] gave the desired β,γ-epoxyketone without formation of this by-product. Isomerization

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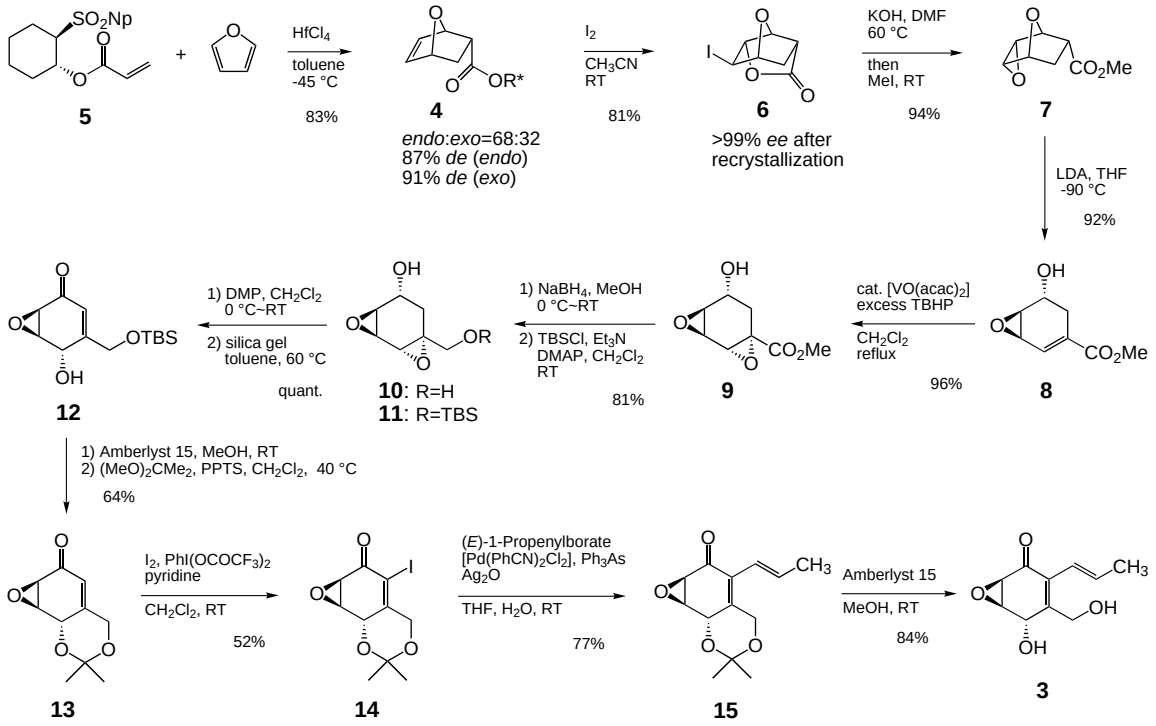
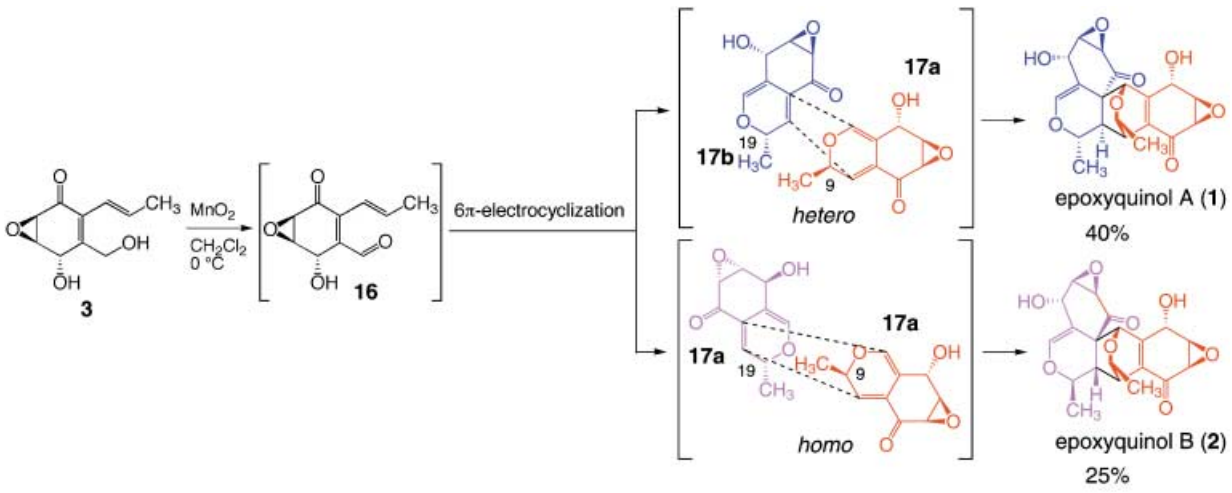


Scheme 2. Synthesis of the monomeric precursor **3** of epoxyquinols A (**1**) and B (**2**). DMAP = 4-dimethylaminopyridine; PPTS = pyridinium toluenesulfonate; for other abbreviations see text.

occurred on treatment of β,γ-epoxyketone with silica gel at 60 °C in toluene for 4 h,[14] affording α,β-unsaturated ketone **12** quantitatively over two steps.

The α-iodonation of cyclohexenone **12** was problematic, and the choice of diol protecting group and iodination reagent was found to be important for the success of this reaction: None of the desired product was obtained on treatment of hydroxy ketone **12** with I_2/DMAP[15] or I_2/trimethylsilylazide ($TMSN_3$)[16] and only a low yield was observed in the reaction using I_2/PhI$(OCOCF_3)_2$/pyridine.[17] On the other hand, the reaction of I_2/PhI$(OCOCF_3)_2$/pyridine with the corresponding acetonide **13** (prepared in 64% yield from **12** over two steps: 1) deprotection of the *tert*-butyldimethylsilyl group with Amberlyst in MeOH, and 2) protection of the resulting 1,3-diol with 2,2-dimethoxypropane) gave the iodinated cyclohexenone **14** in moderate yield. As **14** is labile, it was immediately subjected to the Suzuki coupling reaction with *trans*-1-propenylborate[18] under Johnson's conditions,[19] affording dienone **15** in 77% yield. Cleavage of the acetonide group under acidic conditions provided monomer **3** in 84% yield.

Next the biomimetic oxidative dimerization was examined. After several experiments, it was found that the monomer **3** could be directly oxidized without protection of the secondary hydroxy group. That is, the oxidation proceeded on treatment of epoxycyclohexenol **3** with excess MnO_2[20] in CH_2Cl_2 for



Scheme 3. Biomimetic dimerization approach towards epoxyquinols A (**1**) and B (**2**).

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40 min at 0 °C (Scheme 3), affording hydroxyaldehyde **16** and 2*H*-pyran derivatives **17a** and **17b** which would be formed by 6π-electrocyclization reaction of the former. The dimerization reaction proceeded when the crude oxidized mixture was allowed to stand at room temperature without solvent. After 4 h, epoxyquinols A (**1**) and B (**2**) were isolated in 40 and 25 % yields, respectively. Epoxyquinol A (**1**) is a heterodimer of **17a** and **17b**, which would be generated by an *exo* intermolecular Diels–Alder reaction with the *anti* stereochemistry at the C_9 and C_{19} methyl positions to reduce the steric hindrance at these positions.[2] On the other hand, epoxyquinol B (**2**) is a homodimer of **17a**, which would be generated by an *endo* intermolecular Diels–Alder reaction, also with the sterically favored *anti* stereochemistry at the C_9 and C_{19} methyl positions.[3] In their recent elegant total synthesis of torreyanic acid[21] and jesterone dimer (unnatural product),[22] Porco, Jr. et al. have demonstrated the oxidative dimerization of epoxyquinones, in which only heterodimers were formed. As shown by the dimerization of **3**, not only epoxyquinones, but also epoxycyclohexenones can be oxidatively dimerized to form highly functionalized heptacyclic ring systems, in which both hetero- and homodimerizations occur.

Synthetic epoxyquinols A (**1**) and B (**2**) exhibited identical properties to those of the natural substances (^{1}H NMR, ^{13}C NMR, IR). Comparison of the optical rotation (synthetic epoxyquinol A; $[\alpha]_D^{22} = +60$ ($c = 0.17$, MeOH), natural epoxyquinol A;[2] $[\alpha]_D^{21} = +61.0$ ($c = 0.146$, MeOH), synthetic epoxyquinol B; $[\alpha]_D^{21} = +150$ ($c = 0.060$, MeOH), natural epoxyquinol B;[3] $[\alpha]_D^{21} = +153.0$ ($c = 0.315$, MeOH)) determined the absolute stereochemistry to be as shown in **1** and **2**.

In summary, the first total synthesis of epoxyquinols A (**1**) and B (**2**) has been achieved, and their absolute stereochemistry has been determined. The combination of $HfCl_4$ and the chiral acrylate ester of Corey's auxiliary enables the highly diastereoselective Diels–Alder reaction of furan, which established the correct stereochemistry. All 12 chiral centers of epoxyquinols A and B are controlled by the highly diastereoselective reactions in the route from the initial Diels–Alder product. A diastereoselective synthesis of *endo*-epoxide **7** via iodolactone **6**, and a biomimetic oxidative 6π-electrocyclization, followed by Diels–Alder reaction of the nonprotected diol monomer **3** are other noteworthy features of the synthesis.

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